SYNGAP1-related intellectual disability

SYNGAP1-related intellectual disability is a neurological disorder characterized by moderate to severe intellectual disability that is evident in early childhood. The earliest features are typically delayed development of speech and motor skills, such as sitting, standing, and walking. Many people with this condition have weak muscle tone (hypotonia), which contributes to the difficulty with motor skills. Some affected individuals lose skills they had already acquired (developmental regression). Other features of *SYNGAP1*-related intellectual disability include recurrent seizures (epilepsy), hyperactivity, and autism spectrum disorders, which are conditions characterized by impaired communication and social interaction; almost everyone with *SYNGAP1*-related intellectual disability develops epilepsy, and about half have an autism spectrum disorder.

Frequency

SYNGAP1-related intellectual disability is a relatively common form of cognitive impairment. It is estimated to account for 1 to 2 percent of intellectual disability cases.

Genetic Changes

SYNGAP1-related intellectual disability is caused by mutations in the *SYNGAP1* gene. The protein produced from this gene, called SynGAP, plays an important role in nerve cells in the brain. It is found at the junctions between nerve cells (synapses) and helps regulate changes in synapses that are critical for learning and memory. Mutations involved in this condition prevent the production of functional SynGAP protein from one copy of the gene, reducing the protein's activity in cells. Studies show that a reduction of SynGAP activity can have multiple effects in nerve cells, including pushing synapses to develop too early. The resulting abnormalities disrupt the synaptic changes in the brain that underlie learning and memory, leading to cognitive impairment and other neurological problems characteristic of *SYNGAP1*-related intellectual disability.

Inheritance Pattern

SYNGAP1-related intellectual disability is classified as an autosomal dominant condition, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Almost all cases result from new mutations in the gene and occur in people with no history of the disorder in their family. In at least one case, an affected person inherited the mutation from one affected parent.

Other Names for This Condition

- mental retardation, autosomal dominant 5
- MRD5

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Mental retardation, autosomal dominant 5
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C2675473/

Other Diagnosis and Management Resources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development: What Are Treatments for Intellectual and Developmental Disabilities?
  https://www.nichd.nih.gov/health/topics/idds/conditioninfo/Pages/cure.aspx

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Epilepsy--Overview
  https://medlineplus.gov/ency/article/000694.htm
- Encyclopedia: Intellectual Disability
  https://medlineplus.gov/ency/article/001523.htm
- Health Topic: Autism Spectrum Disorder
  https://medlineplus.gov/autismspectrumdisorder.html

- Health Topic: Developmental Disabilities
  https://medlineplus.gov/developmentaldisabilities.html
- Health Topic: Epilepsy
  https://medlineplus.gov/epilepsy.html

Genetic and Rare Diseases Information Center

- SYNGAP1-related non-syndromic intellectual disability
  https://rarediseases.info.nih.gov/diseases/12558/syngap1-related-non-syndromic-intellectual-disability

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Autism Spectrum Disorder Fact Sheet
  https://www.ninds.nih.gov/Disorders/All-Disorders/Autism-Spectrum-Disorder-Information-Page
- National Institute of Neurological Disorders and Stroke: Epilepsy Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Epilepsy-Information-Page

Educational Resources

- Centers for Disease Control and Prevention: Developmental Disabilities
  https://www.cdc.gov/ncbddd/developmentaldisabilities/
- Centers for Disease Control and Prevention: Facts About Intellectual Disability
  https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/intellectualdisability.pdf
- Disease InfoSearch: Mental retardation, autosomal dominant 5
  http://www.diseaseinfosearch.org/Mental+retardation%2C+autosomal+dominant+5/8828
- MalaCards: syngap1-related intellectual disability
  http://www.malacards.org/card/syngap1_related_intellectual_disability
- Merck Manual Consumer Version: Intellectual Disability
  http://www.merckmanuals.com/home/children-s-health-issues/learning-and-developmental-disorders/intellectual-disability

Patient Support and Advocacy Resources

- American Association on Intellectual and Developmental Disabilities
  http://aaidd.org/
- American Epilepsy Society
  https://www.aesnet.org/
- Autism Society
  http://www.autism-society.org/

- Autism Speaks
  https://www.autismspeaks.org/
- Resource List from the University of Kansas Medical Center: Developmental Delay
  http://www.kumc.edu/gec/support/devdelay.html
- Simons VIP Connect
  https://simonsvipconnect.org/what-we-study/single-genes.html?id=542
- The Arc: For People with Intellectual and Developmental Disabilities
  http://www.thearc.org/

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22SYNGAP1-related+intellectual+disability%22+OR+%22Intellectual+Disability%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28SYNGAP1%29+AND+%28intellectual+disability%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- MENTAL RETARDATION, AUTOSOMAL DOMINANT 5
  http://omim.org/entry/612621

Sources for This Summary

- Aceti M, Creson TK, Vaissiere T, Rojas C, Huang WC, Wang YX, Petralia RS, Page DT, Miller CA, Rumbaugh G. Syngap1 haploinsufficiency damages a postnatal critical period of pyramidal cell structural maturation linked to cortical circuit assembly. Biol Psychiatry. 2015 May 1;77(9):805-15. doi: 10.1016/j.biopsych.2014.08.001. Epub 2014 Aug 13.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25444158
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4326604/
- Clement JP, Aceti M, Creson TK, Ozkan ED, Shi Y, Reish NJ, Almonte AG, Miller BH, Wiltgen BJ, Miller CA, Xu X, Rumbaugh G. Pathogenic SYNGAP1 mutations impair cognitive development by disrupting maturation of dendritic spine synapses. Cell. 2012 Nov 9;151(4):709-23. doi: 10.1016/j.cell.2012.08.045.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23141534
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3500766/
- Clement JP, Ozkan ED, Aceti M, Miller CA, Rumbaugh G. SYNGAP1 links the maturation rate of excitatory synapses to the duration of critical-period synaptic plasticity. J Neurosci. 2013 Jun 19;33(25):10447-52. doi: 10.1523/JNEUROSCI.0765-13.2013.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23785156
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3685838/

- Mignot C, von Stülpnagel C, Nava C, Ville D, Sanlaville D, Lesca G, Rastetter A, Gachet B, Marie Y, Korenke GC, Borggraefe I, Hoffmann-Zacharska D, Szczepanik E, Rudzka-Dybala M, Yis U, Çaglayan H, Isapof A, Marey I, Panagiotakaki E, Korff C, Rossier E, Riess A, Beck-Woedl S, Rauch A, Zweier C, Hoyer J, Reis A, Mironov M, Bobylova M, Mukhin K, Hernandez-Hernandez L, Maher B, Sisodiya S, Kuhn M, Glaeser D, Wechuysen S, Myers CT, Mefford HC, Hörtnagel K, Biskup S; EuroEPINOMICS-RES MAE working group, Lemke JR, Héron D, Kluger G, Depienne C. Genetic and neurodevelopmental spectrum of SYNGAP1-associated intellectual disability and epilepsy. J Med Genet. 2016 Mar 17. pii: jmedgenet-2015-103451. doi: 10.1136/jmedgenet-2015-103451. [Epub ahead of print]
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26989088
- Ozkan ED, Creson TK, Kramár EA, Rojas C, Seese RR, Babyan AH, Shi Y, Lucero R, Xu X, Noebels JL, Miller CA, Lynch G, Rumbaugh G. Reduced cognition in Syngap1 mutants is caused by isolated damage within developing forebrain excitatory neurons. Neuron. 2014 Jun 18;82(6): 1317-33. doi: 10.1016/j.neuron.2014.05.015.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24945774
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4104574/
- Parker MJ, Fryer AE, Shears DJ, Lachlan KL, McKee SA, Magee AC, Mohammed S, Vasudevan PC, Park SM, Benoit V, Lederer D, Maystadt I, Study D, FitzPatrick DR. De novo, heterozygous, loss-of-function mutations in SYNGAP1 cause a syndromic form of intellectual disability. Am J Med Genet A. 2015 Oct;167A(10):2231-7. doi: 10.1002/ajmg.a.37189. Epub 2015 Jun 15.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26079862
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4744742/
- Wang CC, Held RG, Hall BJ. SynGAP regulates protein synthesis and homeostatic synaptic plasticity in developing cortical networks. PLoS One. 2013 Dec 31;8(12):e83941. doi: 10.1371/journal.pone.0083941. eCollection 2013.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24391850
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3877118/

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/syngap1-related-intellectual-disability

Reviewed: May 2016
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services